Pediatric Neurology 52 (2015) 119–124

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Neuromyelitis Optica in an Adolescent After Bone Marrow Transplantation

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ABSTRACT

BACKGROUND: Central nervous system complications of bone marrow transplant are a common occurrence and the differential diagnosis is quite broad, including opportunistic infections, medications toxicities, graft versus host disease, and other autoimmune processes. **PATIENT DESCRIPTION:** We summarize previously reported cases of autoimmune myelitis in post-transplant patients and discuss a 17-year-old boy who presented with seronegative neuromyelitis optica after a bone marrow transplant for acute myeloid leukemia. Our patient had a marked improvement in symptoms after plasmapheresis. **CONCLUSION:** Including our patient, there have been at least eight cases of post-transplant autoimmune myelitis presented in the literature, and at least three of these are suspicious for neuromyelitis optica. Several of these patients had poor outcomes with persistent symptoms after the myelitis. Autoimmune processes such as neuromyelitis optica should be carefully considered in patients after transplant as aggressive treatment like early plasmapheresis may improve outcomes.

Keywords: myelitis, optic neuritis, neuromyelitis optica, bone marrow transplantation, stem cell transplant, acute myeloid leukemia

Pediatr Neurol 2015; 52: 119-124

Introduction

Central nervous system (CNS) complications of bone marrow transplantation (BMT) are common, affecting 14% to 45% of allogenic transplant recipients.[1] Complications vary depending on underlying disease process, the timing relative to transplant, and the immunomodulatory agents used. Immediately after transplant, patients are at risk for seizures and encephalopathies, often related to metabolic derangement, coagulopathy or overwhelming infection. One to 6 months after transplant, neurological problems are more likely to include viral or opportunistic infection from chronic immunosuppression or neurotoxicities from immunomodulatory medications. In particular, most patients are exposed to calcineurin inhibitors, whose neurological sequelae most commonly include dose-dependent tremor and paresthesias but can also in rare instances cause seizures, encephalopathy, and movement disorders.[2]

Several months to years after transplant, recurrence of the primary oncologic process as well as autoimmune disorders have been reported causes of neurological symptoms. In particular, there has been some debate about whether neurological symptoms in posttransplant patients may be a form of graft versus host disease (GVHD). The 2005 National Institutes of Health consensus criteria for GVHD only recognized myositis and polymyositis as distinctive neurological manifestations of chronic GVHD and argued that other peripheral nervous system processes such as neuropathies (including Guillain-Barré and chronic inflammatory demyelinating polyneuropathy) as well as myasthenia gravis could not be considered chronic GVHD unless other more classic manifestations of GVHD were also present.[3] The consensus did not recognize any CNS manifestations of GVHD. The 2009 Consensus Conference in Clinical Practice on chronic GVHD (2009) did review reports

Article History:
Received February 5, 2014; Accepted in final form July 4, 2014
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http://dx.doi.org/10.1016/j.pediatrneurol.2014.07.007

of stroke-like episodes, seizures, encephalopathy, myelopathy, and optic neuritis that authors have attributed to GVHD and subsequently proposed criteria for CNS GVHD (Table 1), most important of which were signs of systemic GVHD and no other explanation for the neurological symptoms.

In addition to GVHD, other autoimmune processes can affect the central nervous system after BMT and such diseases should be considered on the differential when initiating the evaluation and deciding upon treatment for such patients. Here, we describe a case of seronegative neuromyelitis optica (NMO) in a posttransplant patient and review previously published cases of posttransplant autoimmune myelitis.

Patient Description

A 17-year-old right-handed boy with a history of acute myeloid leukemia, 53 days status post sibling-matched BMT and maintained on corticosteroids and cyclosporine, developed several days of progressive urinary retention and ascending lower extremity numbness which led to difficulty walking. Examination was notable for 4/5 weakness in the iliopsoas and hamstring muscles bilaterally but otherwise full strength, 3+ lower extremity reflexes, ankle clonus, absent cremasteric reflexes, and a T8 sensory level. His gait was shuffling and he required two people for support on standing. He had no rash, diarrhea, bloody stools, jaundice, or dry mouth or eyes to suggest GVHD.

T2-weighted and postcontrast T1-weighted magnetic resonance imaging (MRI) of the brain and spine showed patchy nonenhancing hyperintensities within the cervical and thoracic spinal cord as well as subacute punctate hyperintensities in the white matter of the left precentral gyrus but no other intracranial pathology (Fig. 1). Cerebrospinal fluid analysis showed an elevated white blood cell count of 8 cells/mm^3 with a lymphocytic predominance of 98% but was otherwise normal. Oligoclonal bands were absent, the immunoglobulin G index was 0.63 (normal 0.28-0.66) and cytology was negative. Extensive infectious studies of the blood (aerobic, anaerobic and fungal cultures; serum polymerase chain reaction for cytomegalovirus, Epstein-Barr virus, human herpes virus 6, and adenovirus) and CSF (bacterial, fungal, viral & acid fast bacterial cultures; polymerase chain reaction for enterovirus, herpes simplex viruses 1 and 2, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, human herpes virus 6, and adenovirus) were unrevealing. Laboratory studies revealed long-standing pancytopenia, minimally elevated transaminases, and an elevated lactate dehydrogenase. Given concerns for a demyelinating lesion, he was treated with a course of intravenous immunoglobulin (IVIG) 2 grams per kilogram given over 5 days. IVIG was chosen in preference to a steroid pulse as the patient was already on standing steroids for pulmonary complications secondary to the transplant. After the IVIG, he had moderate improvement such that he could walk with a walker. However, urinary retention persisted, requiring intermittent bladder catheterization.

On posttransplant day 91, the patient developed relatively sudden onset of blurry vision and pain with abduction in the left eye. Formal ophthalmology exam on posttransplant day 95 revealed normal optic discs, a left relative afferent pupillary defect and left-sided visual acuity of counting fingers at 4 feet. Orbital MRI showed enhancement of the left optic nerve (Fig. 2). After intravenous methylprednisolone 1 gram daily for 3 days, his left-sided acuity was 20/400. Consultation with a pediatric neuro-immunologist (M.P.G.) then led to the consideration of NMO based on the myelitis, optic neuritis, and brain and spine MRI findings, along with limited recovery despite immunomodulation. Testing for anti-aquaporin 4 antibodies by indirect immunofluorescence in serum and CSF was sent and later returned negative. Starting posttransplant day 115, five sessions of plasma exchange were performed over 2 weeks at a 1:1 ratio with plasma volume. By posttransplant day 124, visual acuity improved to 20/80 in the left eye and he was able to walk independently despite persistent sensory symptoms.

After the plasma exchange, on posttransplant day 138, the patient was started on mycophenolate mofetil for prophylaxis against further relapses but did not tolerate this because of gastrointestinal side effects and persistent transaminitis, which improved after discontinuation. Prophylactic treatment was therefore changed to IVIG (100 g, which was 1 g per kilogram of corrected body weight, infused monthly). Rituximab was considered for prophylaxis but it was felt that the potential risks of prolonged immunosuppression for this particular patient in the setting of recent BMT outweighed the benefits. In addition, per the stem cell transplant protocol, cyclosporine was weaned off by posttransplant day 116 and the standing prednisone (initially started for bronchiolitis obliterans organizing pneumonia, and later maintained given presumptive diagnosis of NMO) was slowly weaned over months and stopped fully at approximately 1 year posttransplant without recurrence of symptoms. At 14 months posttransplant, while the patient was still receiving IVIG but off of all other immunomodulatory agents, repeat testing for anti-aquaporin 4 antibodies in serum was resent and remained negative.

On follow-up visits, he demonstrated mild improvements over time. By 19 months posttransplant (17 months after onset of the myelitis and 16 months after onset of the optic neuritis), his examination was notable for persistent left afferent pupillary defect and visual acuity of 20/70 on the left and 20/40 on the right as well as decreased sensation in both legs, but normal strength and gait. The urinary retention improved and urodynamic studies on posttransplant day 173 showed good bladder capacity without detrusor overactivity. Repeat brain and spine MRIs (on posttransplant days 172 and 391) showed no new lesions.

TABLE 1.
Suggested Criteria for CNS Manifestations of GVHD

1. Concomitant presence of chronic GVHD affecting other organ systems
2. No better explanation for neurological symptoms and signs
3. Abnormalities on brain or spine MRI that correspond with the neurological symptoms
4. Abnormal CSF studies (pleocytosis, elevated protein or IgG levels, oligoclonal bands)
5. Corresponding pathology found on brain biopsy or autopsy specimen
6. Improvement with immunomodulatory therapy

Abbreviations:
CNS = Central nervous system
CSF = Cerebrospinal fluid
GVHD = Graft versus host disease
Criteria 1 and 2 are mandatory and 3 through 6 are supportive. For a definitive diagnosis of GVHD of the CNS, all six criteria must be met and for a "possible" diagnosis, both mandatory and at least two supportive criteria must be met.
Source: Adapted from Grauer et al.[3]

Discussion

Neurological complications of stem cell transplantation are common and vary depending on the original indication for transplantation, the time elapsed since transplant, and the type of medications used in the posttransplant regimen. Because this patient presented within 2 months of transplant, we were initially most concerned for an infectious source of this pathology but an extensive evaluation was unremarkable. In addition, we considered cyclosporine toxicity, but myelitis and optic neuritis have not been reported as a side effect of calcineurin inhibitors. Cerebrospinal fluid (CSF) cytology showed no evidence of recurrent acute myeloid leukemia. In addition, although we considered whether his symptoms might be a manifestation of GVHD, CNS disorders are not considered manifestations of GVHD unless there are other systemic signs of GVHD and there is no other plausible explanation for the CNS condition.[3]